Issues In The Diagnosis of VAP: Definitions for Use In a Prevention Measure

Michael S. Niederman, M.D., FCCP

Chairman, Department of Medicine

Winthrop-University Hospital

Mineola, NY

Professor of Medicine

Vice-Chairman, Department of Medicine

SUNY at Stony Brook

Issues for Discussion

- Diagnosis of VAP: Clinical vs. microbiologic
  - The value of clinical diagnosis
- Problems with quantitative cultures/ microbiologic diagnosis
- Management of VAP with clinical methods
- VAP diagnosis and quality of care
  - Do VAP rates reflect quality of care?
  - If not, what can we measure?
    - Rates vs. patient relevant outcomes and processes of care

Diagnosis of VAP: Clinical vs. microbiologic

The value of clinical diagnosis

Clinical Definition HAP and VAP

- Hospitalized for at least 48 hours
  - Intubated and mechanically ventilated for at least 48 hours at onset : VAP
  - Not intubated and mechanically ventilated for at least 48 hours at onset: HAP
  - Both HAP and VAP can be in ICU
- New, progressive or persistent pulmonary infiltrate on x-ray

AND

- At least 2 of the following:
  - Temperature: <36 ℃ or ≥38.3 ℃
  - WBC <5000 cells/mm^3 or >10,000 cells/mm^3
  - Purulent sputum or endotracheal aspirate (VAP)

AND

- Microbiologic Confirmation (qualitative vs. quantitative cultures)

What About Antibiotic Use?

- Should the therapeutic decision to use antibiotics be part of the clinical diagnostic criteria for VAP?
  - The goal is to reduce antibiotic use, not just the rate of VAP
  - What if antibiotics are used empirically without getting cultures?
    - Would this be considered NO VAP?

Quantitative Bacteriologic Definition of VAP

- Clinical signs of pneumonia PLUS
- Microbiologic confirmation by quantitative cultures
  - > 10^3 cfu/ml on PSB
  - > 10^4 or 10^5 cfu/ml in BAL
  - > 10^6 cfu/ml in endotracheal aspirate
- Maybe accept lower threshold if already on antibiotics for < 48-72 hours.

CLINICAL DIAGNOSIS CAN BE VERY ACCURATE

- A “weighted” clinical diagnosis of VAP, giving 0-2 points each for:
  - Fever, leukocytosis, purulence of secretions, oxygenation, type of infiltrate, growth of tracheal aspirate
- 28 patients, studied with BAL and with Bacterial Index
  - 15 no infection, 13 with infection
- Correlation of BI from bronch BAL and CPIS of 0.84
- If CPIS > 6, 93% with BI $\geq$ 5
- If CPIS $\leq$ 6, all BI < 5
- CPIS > 6 has sensitivity of 93%, specificity and PPV 100%

Pugin et al ARRD. 1991;143:1121-9.

Calculating the CPIS

- Temperature
  - 0 point: 36.5–38.4 C
  - 1 point: 38.5–38.9
  - 2 points: < 36 or > 39
- Blood leukocytes (cells/μL)
  - 0 point: 4000–11000
  - 1 point: < 4000 or > 11000
  - 2 points: > 500 band forms
- Oxygenation (PaO2/FiO2)
  - 0 point: PaO2/FiO2 > 240 or ARDS
  - 2 points: PaO2/FiO2 < 240 and no evidence of ARDS
- Pulmonary radiography
  - 0 point: no infiltrate
  - 1 point: diffuse or patchy infiltrates
  - 2 points: localized infiltrate
- Tracheal secretions (score)
  - 0 point: < 14
  - 1 point: > 14
  - 2 points: purulent sputum
- Culture of tracheal aspirate
  - 0 point: minimal or no growth
  - 1 point: moderate or more growth
  - 2 points: moderate or greater growth

Total score of > 6 points suggests ventilator-associated pneumonia

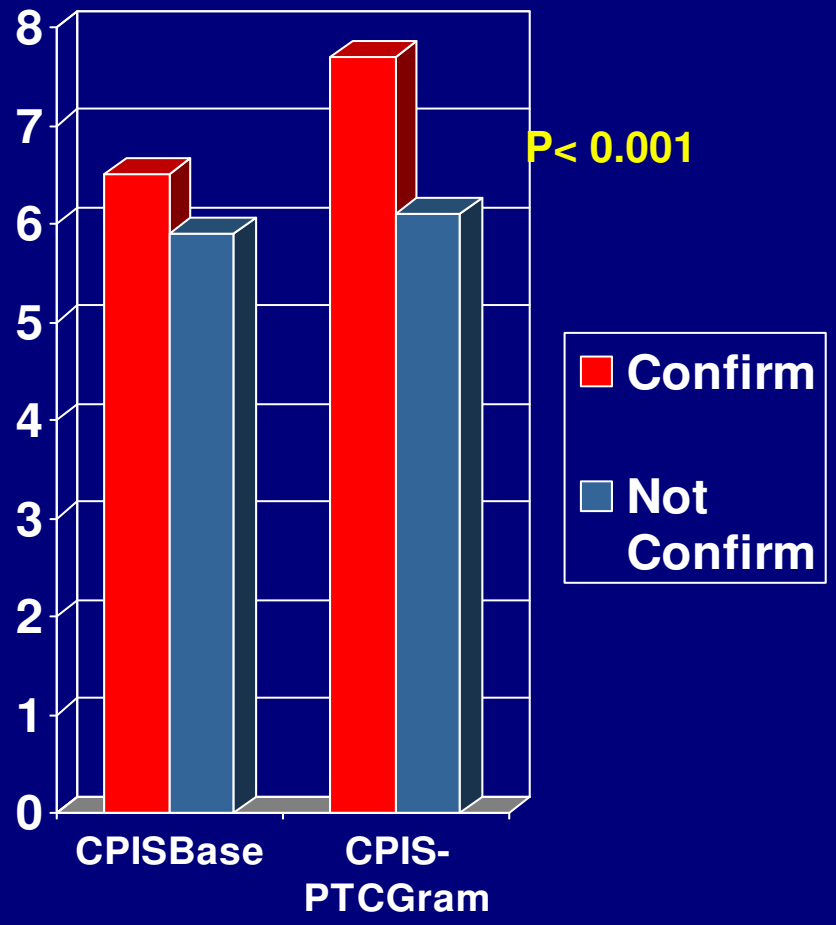
ARDS = acute respiratory distress syndrome

Other Studies of The CPIS: Better Done Prospectively Than Retrospectively

- Compare CPIS to non-bronchoscopic BAL in 145 patients
  - 34 with VAP with CPIS 7.6 vs 4.1 without ($p < 0.001$)
  - Prospective, no bacteriologic data
  - Flanagan et al: Intensive Care Med 2000; 26:20
- Most negative studies use a "modified" score
  - No tracheal aspirate cultures on initial dx
  - No recording of sputum volume by nurses
  - No measurement of band forms
  - Often calculated RETROSPECTIVELY
- Not as valuable if measured retrospectively
  - Applied to 201 patients in the French multicenter study of invasive methods
  - Values on day 1 similar with and without bacteriologic confirmation; not on day 3 with bacteriologic data and radiographic progression (89% sensitivity,47% specificity 84% NPV)
  - Luyt et al: Intensive Care Med 2004; 30: 844

Adding Gram Stain of LRT Secretions Improves the Accuracy of CPIS

- Prospective study of 79 episodes suspected VAP
- 3 steps: inclusion (CPIS); Gram stain of blind PTC and BAL and CPIS; Culture of PTC and qualitative EA and CPIS
- 40 confirmed VAP by BAL as gold standard
- Sensitivity and specificity of CPIS >6 increased if add Gram stain of PTC (78%,56%).
  - Fartoukh et al: AJRCCM 2003; 168: 173-179



Problems with quantitative cultures/ microbiologic diagnosis

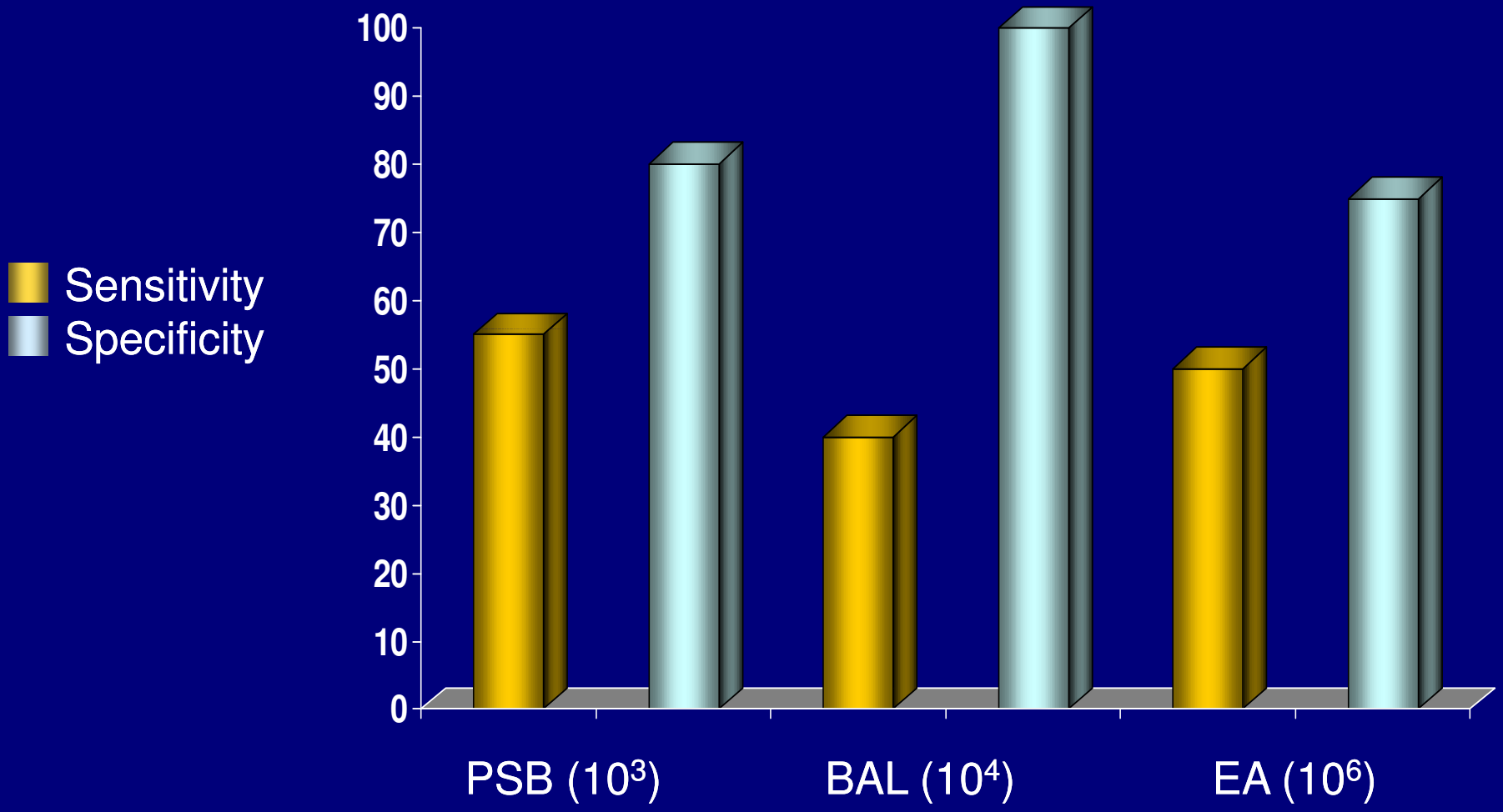
- False positives and negatives with quantitation
- Methodologic problems with quantitative cultures
- Qualitative tracheal aspirates are just as effective

Accuracy of Invasive Bacteriologic Methods

- The autopsy as gold standard
  - 28 MV patients with bronch within 3 days of death
  - Autopsy with full lung dissection: Central and peripheral, 2 samples/segment
  - PSB, BAL, quantitative EA in all patients. 53% off antibiotics. > 48 hours
  - 67% with histologic pn: bilateral, dependent; could be central without peripheral
  - Non-infectious Dx commonly coexist: DAD, fibrosis, infarction; also bronchiolitis, purulent mucus plugs

Marquette et al. Am J Respir Crit Care Med. 1995;151:1878.

Marquette et al.
Am J Respir Crit Care Med. 1995;151:1878.



Sampling Error: Uneven Distribution of the Histologic Stages of VAP

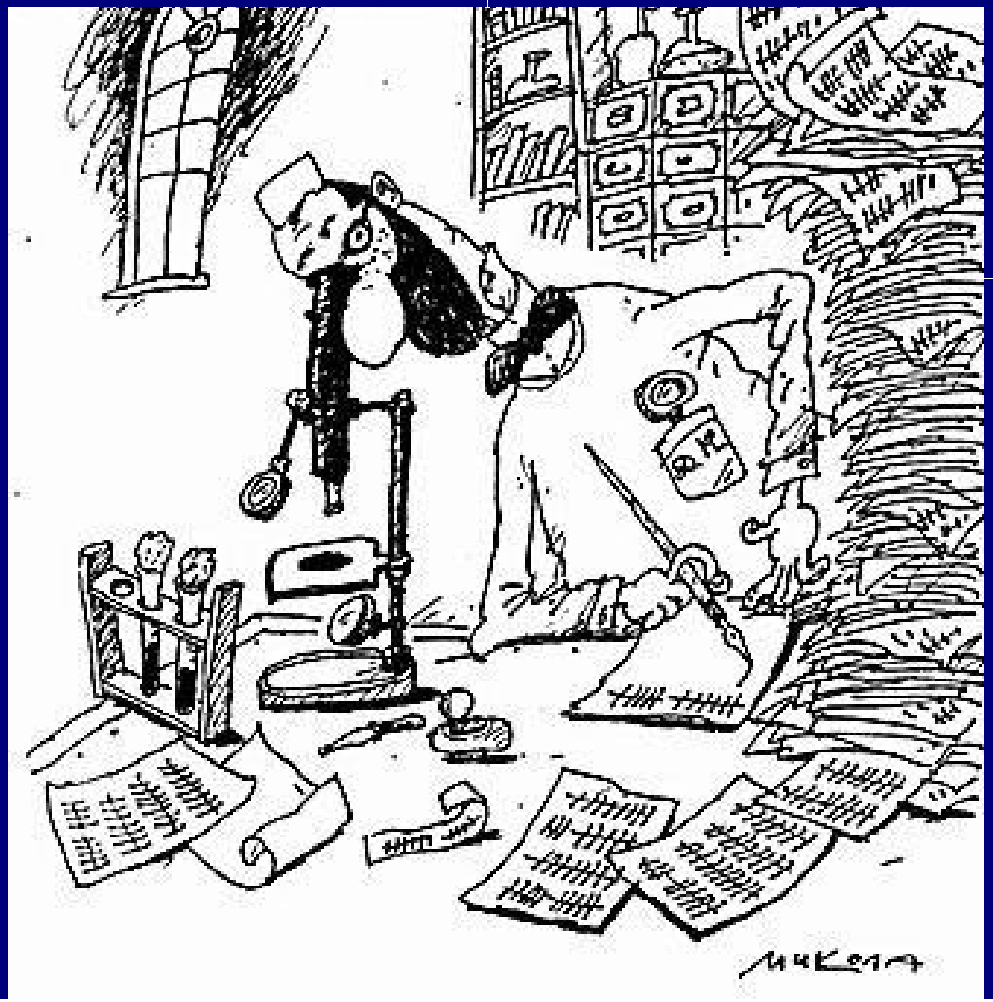
- Pneumonia is in multiple stages of evolution, in multiple sites
  - Potential for sampling error: uninfected site, site of early infection while other sites with advanced infection
- In a piglet model of VAP, found
  - No bacteriologic cutoff could define the presence of histologic pn
  - Histologic lesions unevenly distributed
  - Single organisms unevenly distributed
  - EA more sensitive and discriminating for the organisms causing pneumonia than PSB or BAL

Wermert et al. Am J Respir Crit Care Med. 1998;158:139-47.

Problems with using quantitative microbiology to guide therapy decisions

- Patients with false positive results will receive therapy when colonized
  - 54 quantitative cultures (PSB, BAL) from 32 without suspected pneumonia. 6/23 with positive cults at > threshold. Rodriguez de Castro, et al. AJRCCM 1994; 149: 320
  - 14 patients on prolonged ventilation with no suspicion of VAP. 29/32 lobes sampled with > 10^4 cfu/ml on BAL. Baram et al. Chest 2005; 127:1353-1357.
- Patients with false negative diagnostic testing will not receive timely therapy
  - Methodologic (processing) errors may lead to inaccurate results
  - Antibiotic use creates false negatives. Souweine et al. Crit Care Med. 1998.
  - 246 surgical/trauma patients with BAL.
    - 100 with organisms > threshold (10^5 cfu/ml), 333 at subthreshold concentrations
    - 16% at threshold, 11% at subthreshold had bacteremia (False negative BAL??)
    - Malhotra AK, et al. J Trauma 2008; 65: 580-588

How Is Quantitation Done? Is it Accurate?

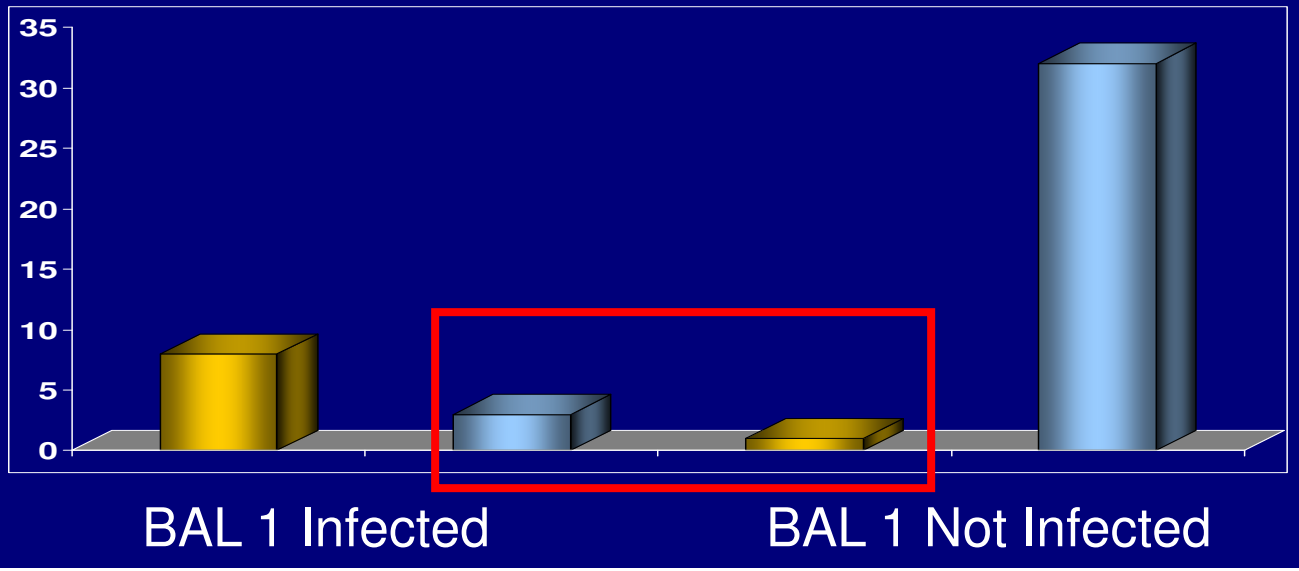


Repeatability of BAL and PSB

- 44 patients, BAL x 2 same site, within 30 min, 3 aliquots (40 mL)
  - 28: both samples sterile; 16 positive: 14 both positive, 2 mixed results
  - Same log in only 5 of 16 with positive samples
    - Gerbeaux et al: Am J Respir Crit Care Med 1998;157: 76-80
- Similar data for repeated PSB
  - 22 patients, 5 PSB's at same site. 100% qualitative reproducitibility
  - 59% of patients with samples> 1 log difference. 3/22 on either side of dx threshold.
    - Marquette CH, et al. Am Rev Respir Dis 1993; 147:211-213.

BAL 2 Infected
BAL 2 Not Infected

(Using 10^4 threshold)



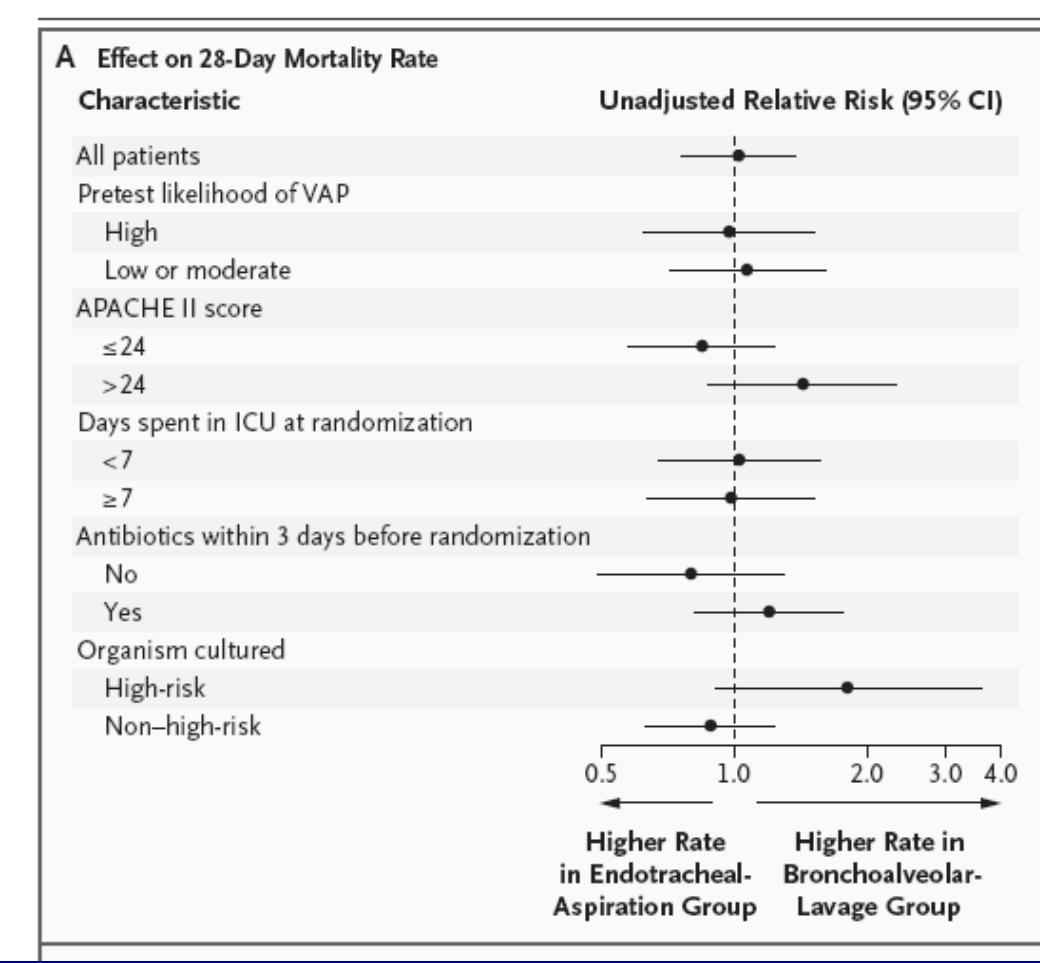
Tracheal Aspirates May Give More True Positives than Quantitative PSB

- Excellent correlation with invasive methods
  - 60 episodes VAP with TBAS, PSB, BAL
    - 90% positive with BAL (10^4), TBAS (10^5)
    - 83% positive PSB (10^3)
      - Woske et al. Critical Care 2001; 5: 167
  - 15 surgical patients with paired TBAS and PSB
    - Often organisms at > 10^4 in TBAS, and not > 10^3 on PSB
    - Same species in TBAS: sens 82%, specificity 79%
      - Aucar et al. Am J Surg 2003; 186
  - 48 patients with non-responding VAP on therapy for at least 72 h: TBAS, PSB and BAL on antibiotics
    - TBAS at 10^5 with sensitivity of 93%, specificity of 80%. Some invasive results may have been false negatives since these cults often +, but below dx threshold
      - Wu et al. Chest 2002; 122: 662

Management of VAP with clinical methods

Canadian Clinical Trial

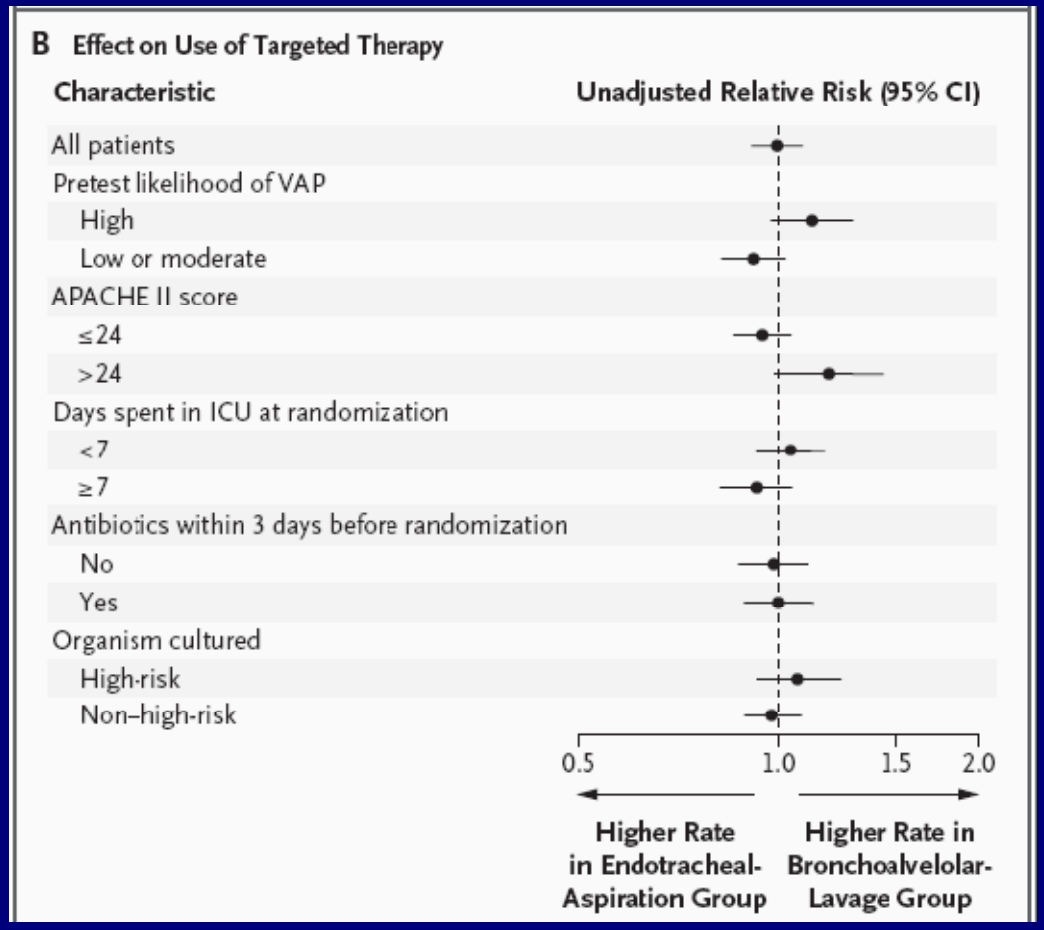
- 740 patients with suspected VAP after 4 days MV.
- Omit known colonization / infection with MRSA or P. aeruginosa
  - BUT 5.1% had MDR pathogens, 14.2% high risk organisms
- Randomized to BAL + quantitative cults or endotracheal aspirate + no quantitation
  - Mono vs. combination rx.
  - No initial withhold of therapy in either group
- No difference in mortality or use of targeted therapy (de-escalation)



Heyland D, et al. NEJM 2006; 355: 2619-2630

Diagnostic Methods and Focused Antibiotic Therapy

- 740 patients, suspected VAP after 4 days ICU
- BAL (quantitative cultures) or EA (non-quantitative cult)
  - Initial rx with meropenem and cipro vs. meropenem
  - Try to exclude if Pseudomonas or MRSA (14% high risk organisms)
- 74% targeted therapy in both groups (discontinuation or modification based on cultures)
  - Positive cults:76% EA; 79% BAL
  - Negative cults:73% EA; 67% BAL
- Heyland et al.: NEJM 2006; 355: 2619-2630.



RCT Data

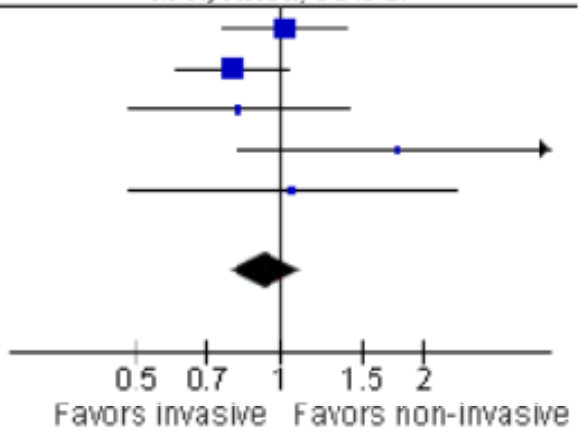
- 5 RCT's comparing invasive vs. non-invasive methods.
  - 3 quantitative vs. qualitative samples, 2 used quantitative methods in both arms
  - No difference in mortality, time in ICU, time on mechanical ventilation, rate of antibiotic change.
    - Berton DC, et al. Cochrane Database Syst Rev 2008.

MORTALITY DATA

Study or Subgroup	Invasive Events	Total	Non-invasive Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CCCTG 2006	69	365	69	374	37.6%	1.02 [0.76, 1.38]
Fagon 2000	63	204	81	209	44.1%	0.80 [0.61, 1.04]
Ruiz 2000	14	37	18	39	9.7%	0.82 [0.48, 1.40]
Sanchez-Nieto 1998	11	24	7	27	3.6%	1.77 [0.82, 3.83]
Solé Violán 2000	10	45	9	43	5.1%	1.06 [0.48, 2.36]
Total (95% CI)		**675**		**692**	**100.0%**	**0.93 [0.78, 1.11]**
Total events	167		184			

Heterogeneity: $Chi^2 = 4.68$, $df = 4$ ($P = 0.32$); $I^2 = 14\%$

Test for overall effect: $Z = 0.76$ ($P = 0.45$)



Management of VAP WITHOUT Quantitative Cultures

- In clinical practice can use a clinical diagnosis (CPIS $\geq$ 6) supplemented by non-quantitative cultures
- All patients need a lower respiratory tract culture prior to antibiotic therapy (tracheal aspirate) but quantitative cultures (non-bronchoscopic or bronchoscopic LRT sample) not necessary.
  - Clinical approach: Culture semi-quantitatively or qualitatively
    - Surveillance cultures may supplement other data to guide accurate empiric therapy
  - Quantitative cultures done with bronchoscopic or non-bronchoscopic samples, are NOT NEEDED.
    - Quantitative cultures may increase specificity for pneumonia dx
    - Are NOT necessary to improve outcome, assure appropriate therapy or de-escalation
    - Their use assures defining only a SUBSET of people with VAP (there are many false negatives)
- A negative LRT culture can be used to de-escalate antibiotics if done in absence of an antibiotic change within 72 hours

VAP diagnosis and quality of care

---Do VAP rates reflect quality of care?

---If not, what can we measure ?

The Argument That VAP Rates Reflect Quality of Care Is Not Logical UNLESS

- VAP is ALWAYS preventable and thus constiutes a Medical Error
  - Then infection rates are a reflection of the quality of care
- Prevention strategies are available, and evidence –based to show efficacy for the diagnosis that is used
- Infection is easily and reproducibly defined
  - Certainly not the case for VAP
- All hospitals have a similar case mix of severity and indigent patients, or else there is an adjustment for these factors
- The hospital is able to REFUSE to give futile care
  - Aggressive and futile care is often complicated by nosocomial infection and in this setting, withholding payment penalizes other non-futile patients

Limitations of The Never Event Concept

- Aiming for zero can have adverse clinical consequences
  - Treating colonization present on admission, and not infection
  - Treating VAT : Is this useful or is it overuse of antibiotics?
- Cost to hospitals can spiral out of control.
  - Diminishing returns after a certain point, and will spend a lot of money for a small (or no) incremental benefit, when resources should be used elsewhere
- Data base research may be flawed by the entry of inaccurate data from public reporting. Low VAP rates do not always lead to better outcomes such as : reduced mortality, reduced antibiotic use, reduced LOS.
- Recommend process measures and population based outcomes
  - Provide positive and negative incentives, not just negative
- Brown J, et al. CID 2009; 49: 743-6.

What Other Approaches Are Possible?

- Adjust for preventability
- Our current model
  - May provide little motivation to improve care
  - High performers are satisfied with status quo
  - Low performers discredit the adjustment model
- Link care actually received to outcomes
  - How many patients with an adverse outcome had an appropriate prevention efforts?
    - Those without prevention effort are defined as avoidable harm
- Pronovost P and Colantuoni E .JAMA 2009; 301: 1273-5

Getting To Zero : A "Sound Bite" and Marketing Idea

- An unhealthy convergence of infection control and quality improvement: 2 different cultures
- Edmond MB. ICHE 2009; 30: 74-76

TABLE. Conceptual Differences Between Hospital Epidemiology and Quality Improvement.

Characteristic	Hospital epidemiology	Quality improvement
Focus	Exploration and analysis	Modification
Primary task	Defining problems and elucidating risk factors	Designing and implementing interventions
Analytic orientation	Population based	Often case based
Primary influences	Science and medicine	Business
Strength	Rigorous methodology and validity	Process design
Approach	Structured, relatively uniform	Encourages innovation
Delivery style	Instructive	Collaborative
Solutions	Targeted: solutions evolve from understanding the problem	Empiric: attempt various solutions and keep what works, discard the rest
Tactics	Data oriented, relatively dull	Flashy campaigns, catchy slogans
Perspective	Long term	Short term, evolving
Tempo	Relatively slow	Relatively fast